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## Original Paper

# Oxaliplatin Added to the Simplified Bimonthly Leucovorin and 5-Fluorouracil Regimen as Second-line Therapy for Metastatic Colorectal Cancer (FOLFOX6)

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**For patients resistant to leucovorin (LV) and 5-fluorouracil (5-FU), the addition of oxaliplatin (85 or 100 mg/m$^2$) to bimonthly LV–5-FU has given a response rate of 20–46%. The highest response rate has been observed with oxaliplatin 100 mg/m$^2$ (FOLFOX2). The present phase II study (FOLFOX6) infused oxaliplatin (100 mg/m$^2$) with LV (400 mg/m$^2$) as a 2-h infusion on day 1, followed by bolus 400 mg/m$^2$ and a 46-h infusion (2.4–3 g/m$^2$) of 5-FU, every 2 weeks. Among the 60 patients treated, 16 (27%) had partial responses (95% confidence interval: 15–38), 27 (45%) had stable disease, 15 (25%) experienced disease progression and 2 (3%) had non-measurable disease. From the start of FOLFOX6, median progression-free survival was 5.3 months and median survival 10.8 months. From the 448 cycles analysed, NCI-CTC grade 3–4 toxicities per patient were: peripheral neuropathy 16%, nausea 7%, diarrhoea 7%, mucositis 5%, neutropenia 24%, thrombocytopenia 2%. Overall 26 (46%) patients experienced grade 3–4 toxicities. Because of toxicity, only 36% of the patients received ≥90% of the scheduled oxaliplatin dose intensity. FOLFOX6 was active in pretreated patients resistant to LV–5-FU and is being investigated as first-line therapy. We are now investigating FOLFOX7, a regimen with a higher oxaliplatin dose intensity and a lower 5-FU dose.** © **1999 Elsevier Science Ltd. All rights reserved.**

**Key words: oxaliplatin, 5-fluorouracil, leucovorin, metastatic colorectal cancer**
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## INTRODUCTION

*In vitro* and *in vivo* preclinical studies on colorectal cancer have shown that oxaliplatin is active against colorectal cell lines and is synergistic with 5-fluorouracil (5-FU) [1]. In phase II trials, oxaliplatin used as a single agent generated a 10% response rate with mild toxicity in patients whose disease progressed whilst under treatment with fluoropyrimidines [2]. Oxaliplatin has also been used in combination with leucovorin (LV) and 5-FU continuous infusion. The first studies concerned a 5-day chronomodulated regimen [3]. The FOLFOX studies on patients whose cancers were resistant to LV–5-FU tested 48-h bimonthly regimens in combination with oxaliplatin at different doses [4]. Figure 1 shows the different FOLFOX regimens. The feasibility study (FOLFOX1) used the bimonthly regimen FOLFUHD with oxaliplatin (130 mg/m$^2$) every other cycle [5]. FOLFOX2 used FOLFUHD in conjunction with oxaliplatin (100 mg/m$^2$) at every cycle [6]. FOLFOX3 combined FOLFUHD with oxaliplatin (85 mg/m$^2$) at every cycle [7, 8]. FOLFOX4 combined the bimonthly regimen LV5FU2 with oxaliplatin (85 mg/m$^2$) at every cycle [8].

The higher response rate with FOLFOX2 than FOLFOX3 and -4, respectively, 46% versus 18–23%, suggested that

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oxaliplatin dose intensity could be critical in the combination of oxaliplatin with 5-FU. The FOLFOX2–3–4 toxicity profiles have two limiting toxicities: grade 3–4 neutropenia (FOLFOX2 39%, FOLFOX3 15 and 20%, FOLFOX4 37%) and specific grade 2–3 sensory neuropathy (FOLFOX2 29%, FOLFOX3 13 and 27%, FOLFOX4 16%). These results led to this study of oxaliplatin at a high dose intensity. In the present study, FOLFOX6, oxaliplatin (100 mg/m$^2$) was added to the new, simplified, bimonthly regimen with high-dose LV followed by bolus and 46-h continuous infusion of 5-FU every 2 weeks [4, 9]. The primary objective of the study was to assess the response rate; secondary objectives were evaluation of tolerance, progression-free survival (PFS) and overall survival.

## PATIENTS AND METHODS

*Inclusion criteria*

Eligibility criteria were: histologically proven adenocarcinoma of the colon or rectum, progression whilst under a bimonthly LV–5-FU regimen, no central nervous system metastases, no second malignancy other than adequately treated *in situ* carcinoma of the cervix or non-melanoma skin cancer, life expectancy of at least 3 months, age >18 years, World Health Organization (WHO) performance status 0–2, metastases outside the irradiation field in patients who had received prior radiation therapy, initial evaluation ≤2 weeks before inclusion, neutrophil count >1500/mm$^3$, platelet count >100 000/mm$^3$ and serum creatinine <300 μmol/l.

Patients were divided into two groups in order to study a population with minimum exclusion criteria which would be more representative of that observed in clinical practice. Group A included patients refractory to the bimonthly, simplified LV–5-FU regimen who had documented progressive disease (PD) under this regimen given alone, age <75 years, alkaline phosphatase <3 times the upper limit of the normal value and bidimensionally measurable lesions—this was the selected population. Group B included patients with at least one of the following criteria: patients refractory to LV–5-FU regimen other than simplified LV–5-FU (LV5FU2 or FUFOLHD), age >75 years, alkaline phosphatase ≥3 times the upper limit of the normal value or non-measurable lesions—this was the population more representative of routine clinical practice. Written informed consent was obtained from all patients.

*Chemotherapy*

The FOLFOX6 regimen consisted of oxaliplatin (100 mg/m$^2$) as a 2-h infusion during the 2-h infusion of LV (DL racemic mixure 400 mg/m$^2$), without mixing, followed by bolus (400 mg/m$^2$ on day 1) and 5-FU 46-h infusion 2.4–3 g/m$^2$. Cycles were repeated at 2-week intervals (Figure 1). Disposable pumps were used for outpatient therapy. During the first two cycles, patients received 2.4 g/m$^2$/46 h of continuous 5-FU, which was increased to 3 g/m$^2$/46 h in subsequent cycles if the maximum toxicity was below National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 2. This regimen was to be continued until progression, if the neutrophil count was >1500/mm$^3$, the platelet count >100 000/mm$^3$ and when toxicity was tolerable (grade 0–2). When NCI-CTC neurological toxicity ≥grade 2 persisted with pain or functional impairment, oxaliplatin was to be discontinued. When thrombocytopenia or neutropenia ≥grade 2 developed, oxaliplatin was to be reduced to 75 mg/m$^2$, and the 5-FU infusion dose was lowered from 3 to 2.4 g/m$^2$ or from 2.4 to 2 g/m$^2$. The same dose adaptation was applied for other NCI-CTC grade 3–4 toxicities. Therapy was discontinued when disease progressed or toxicity was intolerable.

*Study parameters*

Physical examination and complete blood counts were performed at each cycle. Carcinoembryonic antigen (CEA), alkaline phosphatase, lactate dehydrogenase, computed tomography (CT) scans were repeated every four cycles or earlier in the case of clinical deterioration. Only patients with bidimensionally measurable lesions (largest diameter ≥2 cm) on CT scan could be evaluated for tumour responses. Complete response (CR) was defined as the complete disappearance of all assessable disease for at least 4 weeks; partial response (PR) indicated a decrease of at least 50% in the sum of the products of the diameters of measurable lesions, for at least 4 weeks. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% of the lesion, and progressive disease (PD) was an increase of at least 25% or the appearance of new neoplastic lesion(s). For rectal cancers, assessable metastases had to be outside the pelvis. Therapy was discontinued when disease progressed or intolerable toxicity occurred. Weight gain was defined as a ≥2-kg increase of baseline weight. Decreased CEA concentrations were considered a biological effect in patients whose CEA levels had been elevated at baseline but was not used to evaluate the response.

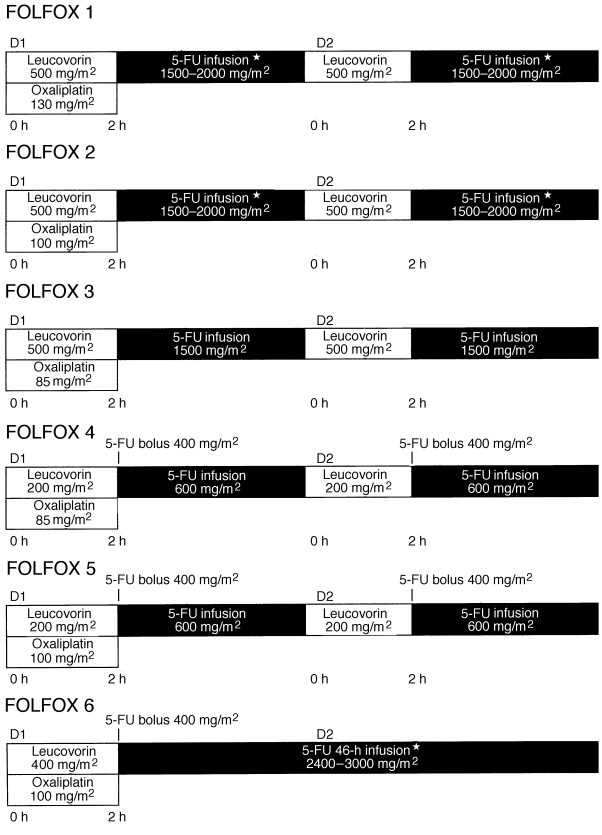


**Figure 1. FOLFOX regimens 1–6. Cycles were repeated every 2 weeks. Oxaliplatin was given every cycle of FOLFOX2–6 and every other cycle of FOLFOX1. *Level 1 for two cycles, then level 2 if toxicity <grade 2.**

*Statistical considerations*

Response duration and survival were calculated using the Kaplan–Meier method from the start of chemotherapy; the end-point was 1 October 1998 [10]. The response duration and PFS were calculated from the date therapy started to the date disease progression was observed.

## RESULTS

*Patient characteristics*

From October 1996 to December 1997, 60 patients were enrolled. Their characteristics are shown in Table 1. 39 patients were assigned to group A and 21 to group B. Among the group B patients, 9 were refractory to the bimonthly, simplified LV–5-FU, 5 of whom were >75 years of age, 3 had alkaline phosphatase ≥3 times the normal value and 2 had non-measurable lesions. 8 other group B patients had PD on the bimonthly regimen with a bolus and low-dose infusion of 5-FU (LV5FU2) [4] with alkaline phosphatase 3 times over the normal value for 2 of them and non-measurable lesions in another; the last 4 group B patients had PD under bimonthly high-dose infusion 5-FU (FOLFUHD) [4], including 1 patient >75 years old.

*Table* 1. *Patient characteristics*

| Characteristic | Group A | Group B | All patients |
|---|---|---|---|
| No. included | 39 | 21 | 60 |
| Median age (range) | 62.3 (35–74) yrs | 61.2 (34–78) yrs | 61.9 (34–78) yrs |
| >75 years old | 0 | 6 | 6 |
| Gender | | | |
| Male | 24 | 12 | 38 |
| Female | 15 | 9 | 22 |
| Primary tumour | | | |
| Colon | 23 | 15 | 38 |
| Rectum | 16 | 6 | 22 |
| Site of metastases | | | |
| Liver | 31 | 16 | 47 |
| Lung | 9 | 4 | 13 |
| Other | 14 | 5 | 19 |
| Involved sites | | | |
| 1 | 27 | 14 | 41 |
| 2 (liver and other) | 9 | 7 | 16 |
| >2 | 3 | 0 | 3 |
| WHO performance status | | | |
| 0 | 22 | 6 | 28 |
| 1 | 14 | 12 | 26 |
| 2 | 3 | 3 | 6 |
| Tumour-related symptoms | | | |
| None | 25 | 13 | 48 |
| Yes | 14 | 8 | 22 |
| Alkaline phosphatase | | | |
| Elevated <3 normal range | 12 | 5 | 17 |
| Elevated ≥3 normal range | 0 | 5 | 5 |
| Elevated CEA | | | |
| Increased >5 ng/ml | 23 | 10 | 33 |
| Increased >100 ng/ml | 15 | 9 | 24 |
| Previous chemotherapy | | | |
| Bimonthly simplified LV–5-FU | 39 | 9 | 48 |
| Other bimonthly LV–5-FU (LV5FU2 or FUFOLHD) | 0 | 12 | 12 |
| Mass diameter | | | |
| ≤5 cm | 14 | 8 | 22 |
| >5 cm | 23 | 11 | 34 |
| Non-measurable lesions | 0 | 3 | 3 |

CEA, carcinoembryonic antigen; LV, leucovorin; 5-FU, 5-fluorouracil.

*Toxicity*

The incidences of the main toxic effects per patient according to NCI-CTC grade [11] are listed in Table 2. Four hundred and forty-eight cycles were evaluated. The median number of cycles administered per patient was 6.7. Neutropenia reached grade 3–4 in 24% of patients, without febrile neutropenia, and was never the reason for discontinuing therapy. Neutropenia did not recur after dose reduction in the patients who experienced grade 3–4 neutropenia under the full 5-FU dose. Grade 3 sensory neuropathy occurred in 16% of patients and 10 of these patients had to stop oxaliplatin because of it before evidence of PD was noted. At the time of the analysis, functional impairment had disappeared in 5 out of 7 patients 2–5 months after oxaliplatin withdrawal. The other grade 3 toxicities observed were thrombocytopenia in 2%, nausea in 7%, diarrhoea in 7% and mucositis in 5% of the patients. Overall, 26 (46%) patients experienced grade 3–4 toxicity. Severe anaphylactic reactions to oxaliplatin were observed in 2 patients after eight and nine cycles, leading to discontinuation of oxaliplatin. One patient was withdrawn from this study for grade 4 immunological thrombocytopenia (antiplatelet autoantibodies) which was not caused by oxaliplatin. Owing to dose reductions, only 36% of the patients received ≥90% of the scheduled oxaliplatin dose intensity during the first four cycles.

*Objective tumour responses*

The objective response rate (ORR) for all patients was 27% (95% confidence interval (CI): 15–38%) (Table 3). For group A, the ORR was 31% (95% CI: 16–46%) and for group B, the ORR was 19% (95% CI: 2–36%). Two CRs were observed in group A. The response rate of patients with liver metastases was 28% and that of those with lung metastases was 20%. Median duration of responses was 8.1 months. SD was observed in 45% of patients (54% in group A and 29% in group B), and PD in 25% of the patients. One group A patient could not be evaluated because of refusal to continue therapy after two cycles. Three progressions were

*Table* 2. *Percentage toxicities per patient (maximum NCI-CTC grade) evaluated for* 448 *cycles given to* 60 *patients*

| | NCI-CTC grade (%) | | | | |
|---|---|---|---|---|---|
| Side-effect | 0 | 1 | 2 | 3 | 4 |
| Nausea/vomiting | 25 | 40 | 28 | 7 | 0 |
| Mucositis | 63 | 20 | 12 | 5 | 0 |
| Diarrhoea | 49 | 22 | 22 | 7 | 0 |
| Sensory neuropathy | 17 | 42 | 25 | 16 | – |
| Hand–foot syndrome | 60 | 25 | 12 | 3 | 0 |
| Anaemia | 80 | 15 | 5 | 0 | 0 |
| Neutropenia | 57 | 5 | 14 | 22 | 2 |
| Thrombocytopenia | 40 | 29 | 29 | 2 | 0 |
| Allergy | 97 | 0 | 0 | 3 | 0 |
| Alopecia | 66 | 37 | 7 | – | – |
| Maximum grade of toxicity | 7 | 15 | 32 | 44 | 2 |

*Table 3. Objective response rates*

| | Group A ($n=39$) | | Group B ($n=21$) | | All ($n=60$) | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| CR | 2 | 5 | 0 | 0 | 2 | 3 |
| PR | 10 | 26 | 4 | 19 | 14 | 23 |
| Stable disease | 21 | 54 | 6 | 29 | 27 | 45 |
| Progressive disease | 5 | 13 | 10 | 48 | 15 | 25 |
| Non-measurable lesions | 1 | 3 | 1 | 5 | 2 | 3 |
| Response rate (95% CI) | 12 | 31 (16–46) | 4 | 19 (2–36) | 16 | 27 (15–38) |

Group A included patients refractory to the bimonthly, simplified LV–5-FU regimen, age <75 years, alkaline phosphatase <3 the normal range and measurable lesions. Group B included all other patients. CR, complete response; PR, partial response; CI, confidence interval.

observed among the 3 group B patients with non-measurable lesions.

*Palliative and biological effects*

Pain disappeared in 9 of the 22 patients (41%) who had had pain at baseline. A weight gain of ≥2 kg was observed in 7 patients (12%). Performance status improved for 6 of the 32 patients (19%) with a baseline performance status ≥1. CEA levels decreased in 44% of patients and the decrease was >50% in 28% of patients with elevated CEA levels at baseline.

*Survival*

The median PFS was 5.3 months and the median survival was 10.8 months from the start of FOLFOX6 (Figure 2). Group A patients had a median PFS of 6.2 months and a median survival of 14.3 months. For group B, median PFS was 4.4 months and median survival 8.8 months.

## DISCUSSION

Second-line metastatic therapy is a newly confronted challenge in advanced colorectal cancer. Limited responses have been achieved with 5-FU infusion, after progression under LV–5-FU bolus treatment [12], or with further 5-FU modulation by LV [13]. Among new drugs, CPT-11 (irinotecan) prolonged the survival of patients with 5-FU-resistant colorectal cancer [14, 15].

The FOLFOX trials have tested bimonthly regimens with oxaliplatin at two different doses: 85 or 100 mg/m$^2$ (Figure 1). The FOLFOX6 study, used the new, simplified, bimonthly LV–5-FU, which combined high-dose LV, and 5-FU bolus on day 1 only and high-dose 5-FU infused over 46 h with a disposable pump for outpatient therapy. This regimen was found to be less burdensome for patients, less costly and at least as active with lower toxicity than the previous bimonthly regimens in which LV infusion had been repeated for 2 consecutive days [9]. We chose to study a population of patients with a minimal number of exclusion criteria which would be more representative of what is observed in clinical practice than a selected population. Group A correspond to a selected population with 'standard' inclusion criteria for a phase II study and, because these patients had progressed on the same LV–5-FU regimen, synergy between 5-FU and oxaliplatin could possibly be demonstrated. An oxaliplatin dose of 100 mg/m$^2$ was chosen because the results obtained in previous studies suggested that there might be a dose-intensity effect on the response rate and because the toxicity profile was also very similar, except for more neutropenia with FOLFOX2 and FOLFOX4. Table 4 summarises the results of the FOLFOX trials (there were two FOLFOX3 studies and FOLFOX5 was not conducted) and the percentages of grade 3–4 toxicities recorded are reported in Figure 3.

*Table 4. Summary of the results obtained with the FOLFOX regimens as second-line therapy*

| Regimen | *n* | Response rate (%) | Median PFS (months) | Median survival (months) |
|---|---|---|---|---|
| FOLFOX1 [6] | 13 | 31 | 6 | 11 |
| FOLFOX2 [6] | 46 | 45.7 | 7 | 17 |
| FOLFOX3 [7] | 30 | 20 | 6 | 10 |
| FOLFOX3 [8]* | 40 | 18.4 | 4.6 | 10.6 |
| FOLFOX4 [8]* | 57 | 23.5 | 5.1 | 11.1 |
| FOLFOX6 (current study) | 60 | 27 | 5.3 | 10.8 |

PFS, progression-free survival. *Updated.

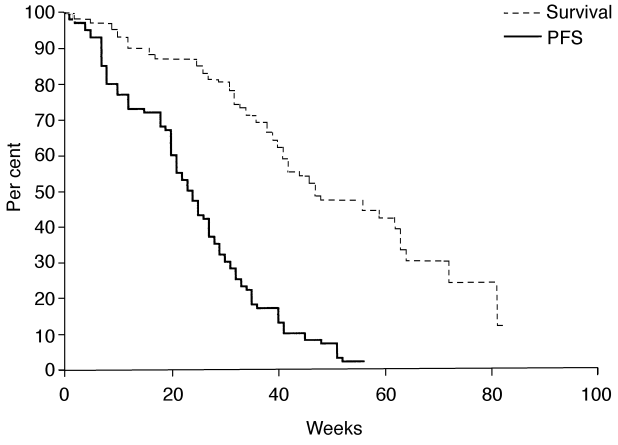


**Figure 2. Survival and progression-free survival curves.**

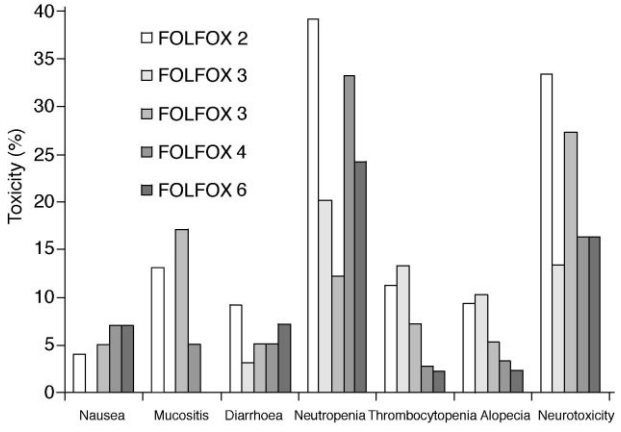


**Figure 3. Percentage of grade 3–4 toxicities with the different FOLFOX regimens (NCI-CTC grading except for FOLFOX2 which had WHO neurotoxicity grade 2–3).**

The responses observed with FOLFOX6 again showed that the combination is active. However, the overall results were not as good as those obtained with FOLFOX2 [6] even if the CI for the responses to FOLFOX2 (95% CI: 31–60) and FOLFOX6 (95% CI: 15–38) overlapped. One explanation for this discrepancy could be the different entry criteria and oxaliplatin dose intensities. The population in the present study was less selected (subgroup B) than that in the FOLFOX2 study. In a retrospective review of oxaliplatin dose intensity, 89% of the patients in the FOLFOX2 study received a dose intensity $\geq 85\,mg/m^2/2$ weeks for the first four cycles versus 59% of those included in FOLFOX6. In the present study, the oxaliplatin dose was lowered to minimise non-neurological toxicity, especially frequent haematological toxicity, whereas in FOLFOX2, only the 5-FU dose was reduced to counter haematological toxicity.

After confirmation of this interpretation of oxaliplatin dose intensity, a new study with a higher oxaliplatin dose and a lower 5-FU dose to limit haematological toxicity will be undertaken (FOLFOX7).

These data, results of a first-line European multicentre randomised trial and those of another study with chronomodulation have demonstrated that oxaliplatin improved the response rates to LV–5-FU regimens and prolonged PFS, and indicate that this combination could well be a major advance in the treatment of advanced colorectal cancer [16, 17].


1. Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol* 1998, **25**(Suppl. 5), 4–12.
2. Machover D, Diaz-Rubio E, de Gramont A, *et al.* Two consecutive phase II studies of oxaliplatin for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. *Ann Oncol* 1996, **7**, 95–98.
3. Lévi F, Misset JL, Brienza S, *et al.* A chronopharmacologic phase II clinical trial with 5-fluorouracil, folinic acid, and oxaliplatin using an ambulatory multichannel programmable pump. *Cancer* 1992, **69**, 893–900.
4. de Gramont A, Louvet C, André T, *et al.* A review of GERCOD trials of bimonthly leucovorin plus 5-fluorouracil 48-h continuous infusion in advanced colorectal cancer: evolution of a regimen. *Eur J Cancer* 1998, **34**, 619–626.
5. de Gramont A, Gastiaburu J, Tournigand C, *et al.* Oxaliplatin with high-dose folinic acid and 5-fluorouracil 48 h infusion in pretreated metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 1994, **13**, 220.
6. de Gramont A, Vignoud J, Tournigand C, *et al.* Oxaliplatin with high leucovorin and 5-fluorouracil 48-h continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997, **33**, 214–219.
7. André T, Louvet C, Raymond E, *et al.* Bimonthly high-dose leucovorin, 5-fluorouracil infusion and oxaliplatin (FOLFOX3) for metastatic colorectal cancer resistant to the same leucovorin and 5-fluorouracil regimen. *Ann Oncol* 1998, **9**, 1–3.
8. André T, Bensmaine MA, Louvet C, *et al.* Addition of oxaliplatin to the same leucovorin and 5-fluorouracil bimonthly regimens after progression in patients with metastatic colorectal cancer. ECCO9. *Eur J Cancer* 1997, **33**(Suppl. 8), S165.
9. Tournigand C, de Gramont A, Louvet C, *et al.* A simplified bimonthly regimen with leucovorin and 5 FU for metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 1998, **17**, 274.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
11. MacDonald J, Haller D, Mayer R. Grading of toxicity. In MacDonald J, Haller D, Mayer R, eds. *Manual of Oncologic Therapeutics*. Lippincott, Philadelphia, 1995, 519–523.
12. Mori A, Bertoglio S, Guglielmi A, *et al.* Activity of continuous-infusion 5-fluorouracil in patients with advanced colorectal cancer clinically resistant to bolus 5-fluorouracil. *Cancer Chemother Pharmacol* 1993, **33**, 179–180.
13. de Gramont A, Louvet C, Bennamoun M, *et al.* Dual modulation of 5-fluorouracil with folinic acid and hydroxyurea in metastatic colorectal cancer. *J Infus Chemother* 1996, **2**, 97–101.
14. Rougier P, Van Custem E, Bajetta E, *et al.* Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998, **352**, 1407–1412.
15. Cunningham D, Pyrhönen S, James RD, *et al.* Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998, **352**, 1413–1418.
16. Levi F, Zidani R, Misset JL, for the International Organization for Cancer Chronotherapy. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *Lancet* 1997, **350**, 681–686.
17. de Gramont A, Figer A, Seymour M, *et al.* A randomized trial of leucovorin and 5-fluorouracil with or without oxaliplatin in advanced colorectal cancer. *Proc Am Soc Clin Oncol* 1998, **17**, 257a.


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